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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/597,808	03/20/2007	Quanlai Song	DVCM0002USA	6589

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EXAMINER	
BLAND, LAYLA D	
ART UNIT	PAPER NUMBER
1623	
MAIL DATE	DELIVERY MODE
02/05/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/597,808	SONG ET AL.	
	Examiner	Art Unit	
	LAYLA BLAND	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/1/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application is a 371 of PCT/US05/04875, filed February 10, 2005, and claims priority to US Provisional Applications No. 60/543,234, filed February 10, 2004, 60/568,587, filed May 5, 2004, and 60/608,522, filed September 8, 2004.

Applicant's election without traverse of Group I, claims 1-25 in part, in the reply filed on November 12, 2008 is acknowledged. Applicant's amendment submitted November 12, 2008, wherein claims 1-23 are amended, is acknowledged. Claims 1-25 are pending and are examined on the merits herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 3, 5, 12, and 23 (and dependent claims) recite the limitation "substituted." Some suitable substituents are exemplified in the specification at page 9, but the definition of substituents is not limited to the examples given. Thus, the claim language permits inclusion of undefined elements into the structure and it is impossible to determine the metes and bounds of the claims.

Claims 4 and 22 recite the limitation "modified sugar." The term is defined in the specification as a compound "containing one or more furanose rings that have been in

some way altered." The claim is indefinite because the specification does not define which alterations of the furanose ring are intended and thus the skilled artisan would not be aware of the metes and bounds of the claim.

Claims 8, 16, and 19 contain the abbreviations CPEP, ACE, TOM, TBDMS, and Fpmp. Where an abbreviation or trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. As noted in MPEP 2111, during patent examination, claims are given their **broadest** reasonable interpretation. It is proper to use the specification to interpret what the applicant meant by a word or phrase recited in the claim. However, it is not proper to read limitations appearing in the specification into the claim when these limitations are not recited in the claim. See *In re Paulsen*, 30 F.3d 1475, 1480, 31 USPQ2d 1671, 1674 (Fed. Cir. 1994) for example. Thus, one of ordinary skill in the art could not ascertain and interpret what the above abbreviations represent and encompasses thereby, and the metes and bounds of the patent protection desired as to the abbreviations. Therefore, an abbreviation is used to identify/describe particular agents and, accordingly, the identification/description is indefinite.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

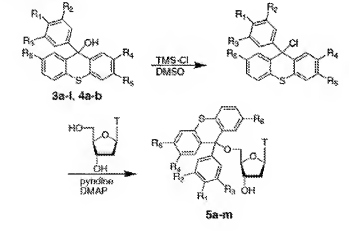
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 3, and 23-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Coleman et al. (J. Org. Chem., 2002, 67 (22), 7641-7648) or Gaffney et al. (J. Chem. Soc. Perkin Trans I 1991, pages 1355-1360, PTO-1449 submitted June 1, 2007), in view of Reddy et al. (US 5,319,079, June 7, 1994).

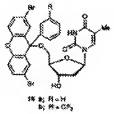
Coleman et al. teach S-pixyl analogues as protecting groups for nucleosides, containing substituents on the 9-aryl ring and on the thioxanthyl backbone [see abstract]. Substituents included methoxy, methyl, fluoro, chloro, and bromo [page 7643, Scheme 2]. The substituted pixyl groups were used to protect a nucleoside, shown below [page 7643, Scheme 3, compounds 5a-m]. Compounds 5a-m were prepared by reaction of thymidine with pixyl chloride as shown below [page 7643, Scheme 3]. The pixyl protecting groups are useful in the synthesis of oligonucleotides with conventional solid-phase protocols [page 7645, Conclusion].

SCHEME 3



Gaffney et al. also teach substituted pixyl protecting groups and exemplify a protected nucleoside wherein positions R^2 and R^7 are bromine, shown below [page

1357, compounds 16a and b]. Compounds 16a and 16b were also prepared by reaction of thymidine with pixyl chloride [page 1359, preparation of 16a and 16b].



The compounds of Coleman et al. or Gaffney et al. each differ from the claimed compounds in that, at positions corresponding to R^2 and R^7, only bromine or hydrogen is exemplified.

Reddy teach that, for preparation of a polynucleotide, pixyl groups having substitution such as alkyl, alkoxy, amino, aminoalkyl, aminoalkoxy, thio, thioalkoxy, hydroxyl, and hydroxyalkyl may be used [column 2, line 61 – column 3, line 3].

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute fluorine, chlorine, or iodine for the bromine substituents in the compounds of Coleman et al. or Gaffney et al. The claimed compounds are very similar structurally and have the same utility as the prior art compounds. See *Graver Tank & Mfg. Co. v. The Linde Air Products Co.*, (USSC 1950) 339 US 695, 85 USPQ 328. The court decision of *Graver Tank* teaches that *the important factor in determining a test for equivalency in a prior art document is whether a person who is reasonably skilled in the art would recognize the equivalency in the compound or composition.* In *Ex parte Wiseman* (POBA 1953) 98 USPQ 277, a difluorinated compound was held unpatentable over the prior art dichloro compound on

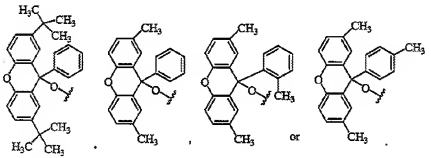
the basis of analogical reasoning. A compound need not be an adjacent homolog or position isomer of a prior art compound in order to be susceptible to a rejection based on structural obviousness; the name used to designate the structural relationship between compounds is not controlling, it is the closeness of that relationship. In *re Payne et al.* (CCPA 1979) 606 F2d 303, 203 USPQ 245. When chemical compounds have "very close" structural similarities and similar utilities, without more, a *prima fade* case of obviousness may be made. *In re Grabiak* (CAFC 1985) 769 F2d 729, 226 USPQ 870. Furthermore, Coleman teaches other substituents for the pixyl group, including methyl, so it would have been obvious to substitute methyl for the bromine substituents.

It would have been further obvious to one of ordinary skill in the art at the time the invention was made to modify the compounds of Coleman et al. or Gaffney et al. such that bromine at R^2 and R^7 are replaced by alkyl, alkoxy, amino, aminoalkyl, aminoalkoxy, thio, thioalkoxy, hydroxyl, or hydroxyalkyl groups. Coleman teaches the importance of substitution directly on the thioxanthyl backbone [page 7644, top of column 2] of the pixyl group, and exemplifies methoxy and bromo substitution on the backbone, as set forth above. Reddy teaches other substituents which are suitable for the pixyl group as used in polynucleotide synthesis. Thus, it would have been obvious to substitute bromine or methoxy as taught by Coleman or Gaffney for the substituents suggested by Reddy.

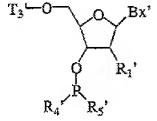
Claims 4-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Coleman or Gaffney in view of Reddy as applied to claims 1, 2, 3, and 23-25 above, and further in view of (Guzaev et al. (WO 2004/011474, February 5, 2004).

Coleman, Gaffney, and Reddy teach as set forth above, substituted pixyl derivatives as protecting groups for nucleosides. Coleman, Gaffney, and Reddy do not exemplify compounds comprising a modified sugar, do not teach compounds having a protected 2'-substituent, do not teach locked nucleic acids or conjugates, and do not teach compounds of formula (II) containing P(Pg)(Pn).

Guzaev et al. teach the following substituted pixyl protecting groups [page 9, Figure], which are appropriate for use in the synthesis of oligomeric compounds such as oligonucleotides and oligonucleosides [claim 47].



Locked nucleic acids are contemplated [page 15], as are compounds having methoxyethoxy, methoxy, O-allyl, or fluoro groups attached to the 2'-sugar position [page 19], as are oligomeric compounds having conjugate groups such as cholesterol [page 25, line 10]. Oligomeric compounds prepared by the process of Guzaev's invention utilize phosphoramidite chemistry [page 33, lines 3-4], utilizing phosphoramidites of the following formula [page 36, top],



wherein R_4 is N(L1)L2, where L1 and L2 are alkyl, R_5 can be a protecting group such as cyanoethyl [page 34, line 32], R_1 is H or an optionally protected sugar substituent group, and T_3 is a hydroxyl protecting group. Preferred hydroxyl protecting groups include DMT and pixyl [page 41, line 5]. Fpmp and other piperidine derivatives are suitable as 2'-O-protecting groups [page 43, lines 14-26].

It would have been obvious to one of ordinary skill in the art to use substituted pixyl protecting groups for nucleoside and nucleotide synthesis, as discussed above, and furthermore to use the substituted pixyl protecting groups for the purposes described above by Guzaev. Guzaev teaches that pixyl is a preferred hydroxyl protecting group and exemplifies some substituted pixyl groups. Coleman, Gaffney, and Reddy also teach substituted pixyl groups for the same utility as pixyl groups. Thus, it would have been obvious to use substituted pixyl protecting groups to prepare the compounds described by Guzaev.

Claims 4-8, 12, 15, 16, and 20-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Coleman or Gaffney in view of Reddy as applied to claims 1, 2, 3, and 23-25 above, and further in view of Reese et al. (US 6,506,894, January 14, 2003).

Coleman, Gaffney, and Reddy teach as set forth above, substituted pixyl derivatives as protecting groups for nucleosides. Coleman, Gaffney, and Reddy do not exemplify compounds comprising a modified sugar with a protected 2'-substituent.

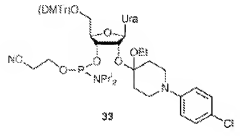
Reese et al. teach a process for solution phase synthesis of oligonucleotides [see abstract]. Protected nucleoside or nucleotide derivatives may be protected at the 3' or 5' position and preferred protecting groups include dimethoxytrityl (DMT) or 9-phenylxanthen-9-yl (pixyl) groups [column 3, lines 45-54]. For ribonucleoside or oligoribonucleotides, the 2'-hydroxy function can be protected by Fpmp or a trialkylsilyl group, or can be a 2'-O-alkyl, 2'-O-alkoxyalkyl, or 2'-O-alkenyl derivative [column 4, lines 55-65]. Compounds containing an H-phosphonate at R_3' and a protecting group at R_5' are taught [column 1, compounds 1 and 2].

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use substituted pixyl groups, as discussed above, in the process of Reese et al. The pixyl group is a preferred protecting group in Reese's method and Coleman, Gaffney, and Reddy teach substituted pixyl groups, as set forth above, having the same utility. Thus, it would have been obvious to use substituted pixyl groups in Reese's method in place of pixyl or DMT protecting groups.

Claims 4, 5, 7, 8, 12-20, and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Coleman or Gaffney in view of Reddy as applied to claims 1, 2, 3, and 23-25 above, and further in view of Lloyd et al. (J. Chem. Soc. Perkin Trans. I, 2000, 165-167).

Coleman, Gaffney, and Reddy teach as set forth above, substituted pixyl derivatives as protecting groups for nucleosides, but do not teach compounds of Formula (II), containing –P(Pg)(Pn).

Lloyd et al. teach that, in the solid-phase synthesis of oligoribonucleotides, DMT and pixyl groups are often used to protect the 5'-terminal hydroxyl function [page 165, Introduction]. To protect the 2'-hydroxy function, the Cpep protecting group was developed [see abstract], as shown below [page 170, compound 33]:



33

It would have been obvious to one of ordinary skill in the art at the time the invention was made to replace the DMT group in the above compound with a substituted pixyl group. Lloyd teaches that either DMT or pixyl are often used for oligoribonucleotide synthesis, and it is also known in the art that substituted pixyl groups can be used for the same utility as pixyl groups. Thus, it would have been obvious to use any of those protecting groups in Lloyd's compound.

Claims 9-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Coleman or Gaffney in view of Reddy as applied to claims 1, 2, 3, and 23-25 above,

and further in view of Lönnberg (Annu. Rep. Chem., Sect. B, 1999, 95, 207-234) and Letsinger et al. (Proc. Natl. Acad. Sci, USA, Vol. 86, pp. 6553-6556, September 1989).

Coleman, Gaffney, and Reddy teach as set forth above, substituted pixyl derivatives as protecting groups for nucleosides, but do not teach locked nucleic acids, 4'-thio nucleic acids, or conjugates.

Lönnberg teaches that oligonucleotide conjugates are of interest because, for example, they could have increased cellular uptake [page 210, Oligonucleotide conjugates]. Lönnberg also teaches that locked nucleic acids are of interest because they exhibit enhanced affinity towards DNA and RNA [page 214, Sugar modified oligonucleotides].

Letsinger teaches cholesteryl-conjugated oligonucleotides which were tethered at the 3'-terminal internucleosidic link[see abstract].

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the substituted pixyl protecting group as discussed above, for the preparation of locked nucleic acids or conjugates because pixyl and substituted pixyl protecting groups are known in the art as protecting groups for nucleosides and nucleotides, as discussed above.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAYLA BLAND whose telephone number is (571)272-9572. The examiner can normally be reached on Monday - Friday, 7:00 - 3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anna Jiang can be reached on (571) 272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Shaojia Anna Jiang/
Supervisory Patent Examiner, Art Unit 1623

/Layla Bland/
Examiner, Art Unit 1623